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RECORD OF ORAL HEARING

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex Parte H. WILLIAM BOSCH, KEVIN D. OSTRANDER
and EUGENE R. COOPER

Appeal 2008-1806
Application 09/190,138
Technology Center 1600

Oral Hearing Held: June 10, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
LORA M. GREEN, *Administrative Patent Judges.*

ON BEHALF OF THE APPELLANT:

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P R O C E E D I N G S

JUDGE SCHEINER: As we go on.

COURT REPORTER: The spelling of the last name, sir.

MR. REID: Certainly. It's R-e-i-d.

COURT REPORTER: Thank you.

MR. REID: Well, there are four obviousness objections at issue, and all of them turn principally upon the primary reference, which is the Patent to Edwards. And as a threshold issue, one of the difficulties in this case was, in my opinion, the legal standard that was applied, because the Patent Office had insisted on a showing of criticality between the claims and the prior art references. I think the correct legal standard was a showing of nonobviousness by the Patent Office in the first instance.

Having said that, I think there's been a pretty basic misunderstanding of Edwards, primarily, and of what the claims actually encompass, and that's why I gave you those cartoons.

In general, there are at least four primary differences between the claimed invention and Edwards and Edwards combined with any of the three secondary references. Those four differences are particle size, crystalline morphology, the aggregate shape, and the requirement that the dispersion returns to a nanoparticulate version.

Starting with particle size, I'll refer you to the first page of the handout that simply shows in rather simplified but not distorted fashion that

the claims really consist of the aggregates, are essentially a two- component thing. The one, the macroscopic, is the respirable aggregate which has a particle size of less than about 100 microns, and within each aggregate are nanoparticulate drug particles which have a size of less than about 1 micron.

In contrast, the cited Edwards reference all along has been asserted to teach the nanoparticulate size. Where I think the basic misunderstanding is, that Edwards and any of the cited references fail to teach those two component features of the claimed invention. Specifically, Edwards is directed to respirable micronized drugs where the mean particle size is 5 to 30 microns, which is quite different than having aggregates of 100 microns and drug particles on a nanoparticulate size scale.

Moreover, Edwards teaches away from the claimed invention. That's because Edwards teaches it's not preferred to have very small particles, and by very small Edwards means about five microns or less. The reason for this is that phagocytes in the lungs will subject the smaller particles to phagocytosis, which completely defeats the point of having respirable particles.

Moreover, Edwards says that larger particles are preferred to aerosolize the drug more efficiently. So based on that difference alone, Edwards clearly teaches away from the claimed invention.

Moving to the second component, which is crystallinity, each of the claims requires the drug to be present in a crystalline nanoparticulate form, that is, the drug itself is a crystal. Now Edwards does not explicitly teach whether the disclosed drug is crystalline or not. However, the methods

disclosed in Edwards to make the respirable particles clearly gives rise to an inference that the particles are amorphous, and this is because the methods specifically disclosed are evaporation of the drug and/or, preferably, a spray drying. Both these methods almost invariably give rise to amorphous drugs.

Moreover, Edwards says that the particles have pores or cavities. They're porous, fluffy particles which are features completely inconsistent with a crystalline drug particle. If you like, I'll give you specific cites, but these are in my brief, too.

JUDGE GREEN: Can you give me a cite for the pores?

MR. REID: Certainly, in Column 5, Lines 64 through 67. So, Edwards discusses different properties of a particle that contribute to aerodynamic lightness. These include a regular surface structure, pores or cavities within the particle.

Along the same access, the third primary difference between Edwards and the claimed invention is the shape of the aggregate. These are the large 100-micron or less aggregates.

The claims require -- each of the claims require the aggregate to be spherically shaped. Edwards takes a different tack: in fact, teaches exactly the opposite. Edwards says that the aerodynamically light particles must be rough, nonsmooth, and nonspherical. I'll refer you to Column 9, Lines 15 through 17 in Edwards.

Edwards, moreover, contemplates particles of any size or shape -- this is the same Column 9, Lines 27 through 28 -- any size or any shape, and at any event nonspherical is epithetical to spherical in the claims. Moreover,

Edwards in describing the invention disclosed therein distinguishes that invention from what it characterizes as prior art smooth and spherical micro-particles. You'll find that discussion in Column 9, Lines 1 through 16. Thus, it's clear that Edwards distinguishes self from prior art by emphasizing nonspherical rough, nonsmooth particles contrast to the claimed invention as well.

In the fourth and final difference, the technical difference between the claimed invention and Edwards is the requirement in each claim that the aggregate, when reconstituted in aqueous liquid medium, return, give rise to the nanoparticulate dispersion from which the aggregates were made.

In Edwards, there can't -- there absolutely cannot be any return to a nanoparticulate dispersion because there is none to begin with. Moreover, Edwards nowhere discusses particles of nanoparticulate size, only microparticles that are five microns or larger. And further, Edwards teaches that the microparticles once in the lungs undergo slow degradation and drug release to the lungs, which is not the same as a return to nanoparticulate drug.

So I submit that based on these differences, Edwards clearly does not teach or suggest all the elements of the claims. Moreover, Edwards clearly teaches away from the claimed invention.

JUDGE GREEN: As to the secondary references, can you just discuss Liversidge?

MR. REID: Sure.

JUDGE GREEN: And just because that's the one that seemed to talk about the nanoparticles --

MR. REID: Yes.

JUDGE GREEN: -- and the crystalline and everything else.

MR. REID: But Liversidge, as you may recognize, is co-owned by the Applicant, the Assignee in this case. Liversidge is directed to noninhalable forms of nanoparticulate drugs. Any drug -- the nanoparticulate drug is crystalline and it has a surface modifier on each drug particle. The Liversidge furthermore teaches that you can spray a dispersion of the nanoparticulate drugs onto sugar spheres or an incipient. The key distinction between Liversidge and this invention is that Liversidge does not disclose or even suggest that these nanoparticles can be used in inhalable forms. Specifically, Liversidge says that you can use these only in parenteral or oral dosage forms, such as an intravenous delivery.

JUDGE GREEN: But does that cause any structural differences to the composition? I mean, the fact that he doesn't disclose that they're not inhalable doesn't mean that they couldn't be, so I'm just curious whether there are structural differences.

MR. REID: The main technical structural difference or issue is converting the liquid dispersion into a respirable aggregate as is claimed. So at the time this application was filed, it was not known or even expected that you could take a dispersion, a liquid dispersion of nanoparticles and convert them into a respirable or inhalable form.

JUDGE GREEN: So would that mean that Liversidge does not teach the spherical particle aggregate to having about the size of 10 microns?

MR. REID: That's correct. In fact, the whole point of Liversidge was to prevent aggregation of nanoparticulate drug.

JUDGE SCHEINER: You're saying that the nanoparticles are put directly into suspension, they're not -- they're never aggregated?

MR. REID: That's correct. In fact, there is discussion in Liversidge about the grinding of bulk drug into nanoparticles, and it's that resulting dispersion which can be used immediately. The whole point of keeping a dispersion with surface -- adhered surface modifiers is to prevent aggregation of these nanoparticles into aggregates.

The aggregation was the main problem for respirable particles. When its uncontrolled aggregation leads to unpredicted -- unpredictable aggregate size -- and as you may know from the application, from the cited literature, control of aggregate size is absolutely essential to targeting different parts of the airway, be it the nasal airway or deep down the lung. Liversidge teaches nothing whatsoever about aggregates or aggregate size.

Did that address your question completely?

JUDGE GREEN: Yes, it did. Thank you.

MR. REID: The third secondary reference is Dalby, which does not address the limitations, the deficiencies of Edwards. Rather, Dalby is concerned with aerosolized compositions of a specific drug, namely, Beclomethasone. Dalby does not teach that the particles -- or does not clearly teach the particles are aerosolized in a crystalline form.

Moreover, Dalby does not address the spherical aggregates that are claimed and Dalby, furthermore, does not teach or suggest that aggregates if formed can be reconstituted into nanoparticulate drug as the present claims require. Moreover, Dalby teaches away again from the invention. This is because Dalby strongly prefers the drug stays in solution. The reference teaches this at discussion from Column 4, Line 59 through Column 5, Line 2.

Specifically, Dalby says the drug should stay in solution to prevent, one, crystal growth problems; two, to maximize drug delivery; and third, perhaps most important, to minimize oral pharynx deposition. And, these three features that are encouraged by Dalby are apathetical to the presence of crystalline drug nanoparticles as in the claims.

And, finally, the fourth reference is more or less a reference work, Goodman and Gilmans, or the discussion of a particular drug administration route. In any event, Goodman does not address any of the deficiencies I highlighted earlier with Edwards, Liversige or Dalby.

So keep these clear-cut differences in mind, and with at least two of main references teaching away from the invention, the claims are nonobvious in light of these four references. Thank you.

JUDGE SCHEINER: Do you have anything further?

JUDGE GREEN: Nothing, thank you.

JUDGE SCHEINER: Thank you for coming in.

MR. REID: Quite welcome. Appreciate your time. Thank you.

(Whereupon, the hearing concluded on June 10, 2008.)